Health and Economic Outcomes of the Emergence of Third-Generation Cephalosporin Resistance in Enterobacter Species

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Background: This study evaluated the clinical and economic impact of the emergence of third-generation cephalosporin-resistant Enterobacter species.

Methods: Mortality, length of hospitalization, and hospital charges were examined in a cohort that was selected from a group of 477 patients with initial cultures that yielded a third-generation cephalosporin–susceptible Enterobacter species. Case patients (n=46) had subsequent cultures yielding a third-generation cephalosporin–resistant Enterobacter species. Control patients (n=113) who did not develop resistance were matched to cases on site of Enterobacter infection and length of hospitalization prior to isolation of the initial susceptible organism. Multivariable analyses were used to adjust for confounding.

Results: Twenty-six percent of cases died vs 13% of controls (P=.06). The median total hospital stay for cases was 29.5 days (interquartile range [IQR], 20-60) and 19 days for controls (IQR, 13-27; P<.001). The median hospital charge for cases was $79,323 (IQR, $34,546-$161,384) and for controls was $40,406 (IQR, $18,470-$79,005; P<.001). After adjusting for comorbidities, severity of illness, intensive care unit admission, surgery, transfer from another hospital, sex, and age, emergence of resistance was associated with increased mortality (relative risk, 5.02; P=.01), hospital stay (1.5-fold, P<.001), and hospital charges (1.5-fold, P<.001). Emergence of resistance had a median attributable hospital stay of 9 days and an average attributable hospital charge of $29,379.

Conclusions: Emergence of antibiotic resistance in Enterobacter species results in increased mortality, hospital stay, and hospital charges. Minimizing resistance in Enterobacter species should be a priority.

Arch Intern Med. 2002;162:185-190

Resistance to antimicrobial drugs is a growing health and economic concern. Rates of resistance in hospital-acquired gram-positive and gram-negative infections have risen dramatically over the past decade. Infections caused by resistant organisms are thought to result in higher morbidity and mortality, prolonged hospitalization, and increased costs compared with infections caused by sensitive strains; however, few studies have examined quantitatively the health and economic impact of the development of resistant organisms.

Enterobacter species are common nosocomial pathogens; they represent 6% of all hospital-acquired isolates and 11% of all pneumonia isolates. Recent data show that they are the most frequently isolated gram-negative organisms in intensive care unit (ICU) bloodstream infections and they are the third most common pathogen isolated in cases of ICU pneumonias. Resistance in Enterobacter isolates is common. In US hospitals reporting to the National Nosocomial Infection Surveillance (NNIS) System, the rate of third-generation cephalosporin resistance in ICU infections caused by Enterobacter species between January 1999 and December 1999 was 34%. Resistance to β-lactam antibiotics is most frequently mediated by hyperproduction of inducible chromosomal AmpC β-lactamase. Enterobacter isolates initially may test susceptible to β-lactam antibiotics in vitro, but the emergence of resistance occurs during therapy because of increased β-lactamase production. The emergence of third-generation cephalosporin resistance occurs in an average of 10% of patients receiving antimicrobial therapy and in up to 20% of patients treated with third-generation cephalosporins.

Patients from whom resistant Enterobacter species are cultured have an increased risk of mortality. However, these patients represent two populations: those in whom a resistant organism is detected in baseline cultures and those in whom resistance emerges after the detection of a susceptible organism. In the case of Pseudomonas aeruginosa, there is evidence that outcomes of patients who develop antimi-
PARTICIPANTS AND METHODS

HOSPITAL SETTING AND STUDY DESIGN

Beth Israel Deaconess Medical Center, West Campus, is a 320-bed urban tertiary care teaching hospital in Boston, Mass. It has 24 ICU beds and approximately 11,000 patient admissions per year; there are no pediatric or obstetric patients.

We conducted a nested matched cohort study of patients who had clinical cultures positive for *Enterobacter* species and who were treated with antimicrobial agents. The cohort was drawn from a group of 477 patients admitted to the hospital between September 1, 1994, and August 31, 1997, from whom an *Enterobacter* species that was susceptible to third-generation cephalosporin antibiotics was cultured. This group of patients has been described elsewhere. The 49 patients who had subsequent cultures that grew an *Enterobacter* species that was resistant to third-generation cephalosporins were classified as cases and entered our cohort at the time that the third-generation cephalosporin–resistant *Enterobacter* species were cultured. Controls were chosen from the original 428 patients who had cultures positive for a susceptible *Enterobacter* species strain but no subsequent cultures that yielded a resistant strain. Controls were individually matched to cases on 2 parameters: the anatomic site from which the *Enterobacter* species was isolated and the length of hospital stay prior to detection of the initial susceptible organism. In addition, controls were required to have stayed in the hospital for at least the same duration as the time to isolation of a resistant strain for the matched cases. Up to 3 controls were matched to each case; only exactly matched controls were included. Three outcomes were studied: in-hospital mortality, length of hospital stay, and hospital charges.

DATA COLLECTION AND MICROBIOLOGY

Patient characteristics and microbiology data were prospectively collected in the hospital data repository. Variables relating to comorbidities, hospital events, and cost were extracted from administrative, accounting, and laboratory databases. All recorded hospital events occurred prior to the patients’ entry into the cohort. Severity of illness was classified by the criteria of McCabe and Jackson and was assessed at the time of cohort entry. Patients were categorized into 3 groups: those with rapidly fatal illnesses who were expected to die within 2 weeks (score=1), those with ultimately fatal diseases who were expected to live less than 5 years (score=2), and those with nonfatal illnesses (score=3). This information was extracted from patient charts. Data were then compiled into a single data set using a relational database management system (Access; Microsoft Corp, Redmond, Wash).

Clinical *Enterobacter* isolates were collected by the clinical microbiology laboratory between September 1, 1994, and August 31, 1997. *Enterobacter* species were identified using the Gram-Negative Identification Panel Type II (Dade International Inc, West Sacramento, Calif). In vitro susceptibility was tested by microbroth dilution (MicroScan, Dade International Inc).

Emergence of resistance was defined as the subsequent detection of a positive culture for a third-generation cephalosporin–resistant *Enterobacter* species from a patient with previous cultures from the same site yielding a susceptible *Enterobacter* isolate. The organisms had a change in interpretive class and at least a 4-fold increase (2 dilutions) in minimal inhibitory concentration (MIC) relative to the baseline isolate. The National Committee for Clinical Laboratory Standards susceptibility thresholds for third-generation cephalosporins were used as breakpoints to classify strains as susceptible or resistant to third-generation cephalosporins. Isolates with MIC values indicative of intermediate susceptibility (MIC=16-32 for ceftriaxone and MIC=16 for ceftazidime) were considered resistant.

STATISTICAL ANALYSIS

Statistical analyses were performed with SAS software (version 7; SAS Institute Inc, Cary, NC). Comparison of case and control variables was performed using the 2-sided Wilcoxon rank sum test for continuous variables, the Cochran-Mantel-Haenszel estimate for matched data for binary variables, and the $\chi^2$ trend test for ordinal variables.

Univariate analysis of the association between individual variables and the 3 outcomes studied was performed using matched regression models that examined the individual variable of interest. Mortality was analyzed with conditional logistic regression. Hazard ratios from the conditional logistic regression models are presented as relative risks (RRs). Length of stay and hospital charges were log transformed to achieve a normal distribution and analyzed with linear regression models with an absorbed variable to account for matching. The coefficients were converted to RRs using an exponential transformation. The discharge date used for the length of stay analysis for patients who died was the date of death.

Three separate multivariable analyses were performed for the 3 outcomes using conditional logistic regression for the analysis of mortality and linear regression for the analysis of length of stay and hospital charges. Variables with a $P$ value of less than .1 in the univariate analysis were included in the corresponding multivariable analysis. All predictors were checked for confounding and collinearity. Possible confounding variables were added one by one into the model, and if this resulted in a change in the coefficient estimate of a covariate of 10% or more, the variable was left in the model. Effect modification between variables was evaluated by testing appropriate interaction terms for statistical significance. The final regression models were analyzed for overfitting by the bootstrap method (1,000 bootstrap samples of all the data were used).

All statistical tests were 2-tailed; $P \leq .05$ was considered significant.
RESULTS

Of the 477 patients with initial cultures that grew a third-generation cephalosporin–susceptible Enterobacter species, 49 had subsequent cultures that grew a third-generation cephalosporin–resistant strain and were eligible to be cases in the cohort. For 32 cases, exactly matched controls were found at a 1:3 ratio. For 3 cases, 2 exactly matched controls were found for each case. For 11 cases, 1 exactly matched control was found for each case. Three cases did not have suitable matches and were excluded from the analysis. Thus, our nested cohort included 46 cases who were matched to 113 controls who did not have emergence of resistance. One hundred seven isolates were identified as Enterobacter cloacae, 47 as Enterobacter aerogenes, and 5 as Enterobacter agglomerans; there were no significant differences in the number of each species between cases and controls (P=.87). The majority of isolates were from the respiratory tract (44%), followed by wounds (20%), effusions (18%), blood (13%), and urine (5%).

Patient characteristics are shown in Table 1. There were no significant differences in age, sex, or comorbidities between cases and controls. The mean age of the cohort was 63 years. Sixty-two percent of patients were men. Both cases and controls had a median of 2 comorbidities. Specific comorbidities occurred with similar frequencies among cases and controls. The median length of stay prior to isolation of an Enterobacter species was similar for cases and controls (5.5 and 5.0 days, respectively; P=.76). The study population included a large proportion of severely ill patients; 29.6% were transferred from another institution, 67.9% underwent a major surgical procedure, and 68.6% were admitted to the ICU before inclusion in the study. Admission to the ICU was the only variable that differed significantly between cases and controls. Eighty percent of cases compared with 64% of controls were admitted to the ICU before entry into the cohort (P=.02). There were no significant differences in the McCabe severity of illness scores between cases and controls. The majority of patients (63.5%) had ultimately fatal illnesses; 6.3% had rapidly fatal illnesses and 30.2% had nonfatal illnesses.

MORTALITY

Twenty-seven of the 159 patients in the cohort died in the hospital (case fatality rate, 17%). Mortality was higher
Results of a multivariable analysis for mortality are shown in Table 2. Emergence of third-generation cephalosporin resistance was associated with increased length of hospital stay (RR, 2.83; P < .001). Other significant univariate predictors of increased length of hospital stay included underlying cardiovascular disease (RR, 1.99; P = .04), underlying hepatic disease (RR, 2.47; P = .01), low McCabe score (RR, 1.32; P = .007), ICU admission while in the hospital (RR, 1.73; P = .001), major surgery (RR, 1.85; P = .01), and transfer from another institution (RR, 2.47; P = .007). The results of the multivariable analysis for length of hospital stay are shown in Table 3. After adjusting for confounding, emergence of resistance to third-generation cephalosporins remained a strong predictor of increased hospital stay. A 1.47-fold longer hospital stay occurred in patients who had emergence of a resistant Enterobacter species compared with those who did not (P < .001).

### LENGTH OF HOSPITAL STAY

The median total length of hospital stay for the cohort was 21 days (interquartile range [IQR], 15-33); median length of stay was longer for cases (30 days; IQR, 20-60) than for controls (19 days; IQR, 13-27; P < .001). Results of the crude analysis for the association of patient variables with length of stay are shown in Table 2. Emergence of resistance had a median attributable length of stay of 9 days. After adjusting for confounding, emergence of resistance to third-generation cephalosporins remained a strong predictor of increased mortality (RR, 5.02; P = .01). Low McCabe score (RR, 3.41; P = .02), ICU admission during hospitalization (P = .01), and increased number of underlying comorbidities (RR, 2.53; P = .04) were also associated with increased in-hospital mortality.
HOSPITAL CHARGES

Median hospital charges for cohort members were $46010 (IQR, $22098-$96417). The median hospital charges were significantly higher for cases ($79323; IQR, $34546-$161385) than for controls ($40406; IQR, $18470-$79005; P < .001). Results of a crude analysis for the association of the cohort characteristics with hospital charges are shown in Table 2. Emergence of third-generation cephalosporin resistance was associated with increased hospital charges (RR, 1.85; P < .001). Other significant univariate predictors of increased hospital charges included underlying cardiovascular disease (RR, 1.56; P = .02), underlying hepatic disease (RR, 1.81; P = .005), low McCabe score (RR, 2.39; P = .006), ICU admission during hospitalization (RR, 3.06; P < .001), major surgical procedure during hospitalization (RR, 1.80; P < .001), and transfer from another institution (RR, 1.63; P = .003). The results of the multivariable analysis of hospital charges are shown in Table 3. After adjusting for confounding, emergence of resistance to third-generation cephalosporins remained a significant predictor of increased hospital charges. A 1.51-fold increase in hospital charges occurred in patients who had emergence of a resistant Enterobacter species compared with those who did not (P < .001). The average hospital charge for controls in our cohort was $57 606 and after adjusting for confounding, a 1.51-fold increase in hospital charges occurred; therefore, emergence of resistance had an average attributable hospital charge of $29 379 per patient in our cohort. Underlying hepatic disease (RR, 1.35; P = .04), low McCabe score (RR, 1.33; P = .003), ICU admission during hospitalization (RR, 2.18; P < .001), having a major surgical procedure while in the hospital (RR, 1.43; P = .001), and transfer from another institution (RR, 1.41; P = .003) were also significant predictors of increased hospital charges.

ICU PATIENTS

To explore the issue of whether increased mortality, length of hospital stay, and hospital charges were driven by admission to the ICU as opposed to the emergence of resistance, we performed a subgroup analysis of patients who had been in the ICU before inclusion in the study. In this population of critically ill patients, the effects of resistance on length of stay and hospital charges remained significant. Patients with emergence of resistance had a longer median hospital stay (36 days; IQR, 25-64) than patients without resistance (22 days; IQR, 16-32; P < .001). They also had higher median hospital charges ($116 182; IQR, $61 618-$172 260) vs $61 060; IQR, $40 595-$96 439; P = .002). Mortality was higher in patients who developed resistance than in those who did not (case fatality rate, 32% vs 21%), but this difference did not reach statistical significance (P = .19).

Recent epidemiologic data show an increase in the frequency of isolation of bacteria that are resistant to antimicrobial agents. To form a rational understanding and approach to controlling the development and spread of antimicrobial resistance, quantification of the medical and economic consequences of antimicrobial resistance is essential. This information is important for clinicians, infection control practitioners, and even more so for policymakers. Several studies have demonstrated adverse health outcomes in patients with resistant organisms although the magnitude may vary based on the organism, the site of isolation, antimicrobial resistance patterns, and the mechanism of resistance. Estimates of the costs of resistance are high—the US Congress has reported that the annual additional hospital cost of resistance total at least $1.3 billion; however, data on costs of resistance attributable to individual organisms are sparse.

This study specifically addresses the issue of emergence of third-generation cephalosporin resistance during hospitalization. Other studies have shown that patients with nosocomial isolation of a resistant organism have worse outcomes than patients who enter the hospital with a resistant organism, but data are limited. Previous studies have focused on mortality due to bacteremia, but bloodstream infection comprises less than 10% of the total infections caused by Enterobacter species. Moreover, data on other outcomes such as length of hospital stay and hospital charges may be needed to delineate the adverse consequences of the development of antimicrobial resistance and may provide the basis for adjusting resource allocation to prevent resistance. In this study, we analyzed positive cultures originating from several different anatomic sites to demonstrate that adverse outcomes result from involvement of sites other than the bloodstream. Our evaluation of the length and cost of hospitalization further defines the effect of resistance on patients’ health outcomes.

In this study, we have shown that emergence of resistance to third-generation cephalosporins in Enterobacter species is associated with severe adverse outcomes. In both univariate and multivariable analyses, emergence of resistance was associated with increase in mortality (increased 5-fold), length of hospital stay (increased 1.4-fold), and hospital charges (increased 1.5-fold). In this cohort, the incidence of emergence of third-generation cephalosporin resistance was 10.3%. If the average attributable cost of resistance was $29 379, then measures directed at preventing resistance that cost up to an average of $29 38 per patient with Enterobacter species isolated would be cost saving in our hospital.

There are several possible reasons for our findings that emergence of resistance leads to poor outcomes. More serious or deep-seated Enterobacter species infections with a higher organism burden may provide circumstances that are more favorable to the selection of resistant strains, and adverse outcomes may be the consequence of a more severe initial infection. While we believe that there is likely a correlation between the size of inoculum, the development of resistance, and the persistence of infection, disentangling the individual effect of these factors as causes of adverse outcomes is not possible given the data available for this study. Another explanation, which has been supported by other studies, is that antimicrobial resistance leads to inadequate or delayed antimicrobial therapy, either because patients are not changed from ineffective empiric regimens to therapies that are effective against the resistant organism or because therapeutic options are limited.

Two factors may have caused underestimation of the effect of emergence of resistance on outcomes. First, it is likely that the development of a resistant organism in...
a given patient preceded the detection of the organism in clinical cultures; this would decrease the number of days and charges attributable to the development of resistance. Second, there may have been patients who developed resistance that was not detected on repeated cultures, leading to misclassification of cases as controls.

Differentiating between infection and colonization may be difficult in a retrospective analysis; moreover, the state of being colonized or infected may change over time. All patients in our study were treated with antibiotics for presumed infection. Although it is possible that some misclassification of infection and colonization might have occurred, by matching on the site of isolation of the organism and including only patients treated for infection, this bias was minimized.

There are some possible limitations to this study. First, an analysis of hospital charges most closely reflects the hospital’s perspective of the costs of emergence of resistance. The costs to patients, third-party payers, and society are under-estimated by our analysis because we did not quantitate the medical costs accrued beyond hospitalization or non-direct medical costs. Second, we did not perform a molecular analysis of the *Enterobacter* species isolates to confirm that, for a given patient, the susceptible and resistant *Enterobacter* species strains were related. However, from a practical perspective this is of little importance. Third, it is difficult to make generalizations regarding the effects of the emergence of resistance in other organisms based on the results of this study. However, effects of similar magnitudes were found for emergence of resistance in *Pseudomonas*.

Further evaluation of the effects of resistance on patient outcomes for other organisms must be undertaken.

Given the health and economic costs associated with emergence of third-generation cephalosporin resistance in *Enterobacter* species that we have demonstrated, efforts to minimize resistance in *Enterobacter* species should be a priority. Because other studies have shown that resistance is most strongly associated with exposure to third-generation cephalosporins, we suggest that these agents be used with caution in the treatment of infections caused by susceptible *Enterobacter* species. In addition, patients with *Enterobacter* species infections should be monitored carefully with frequent clinical cultures to detect the emergence of resistance. How the use of combination therapy or of individual advanced β-lactams might affect rates of emerging resistance to third-generation cephalosporins remains to be fully elucidated.

We conclude that the emergence of antibiotic resistance in *Enterobacter* species is associated with significant adverse outcomes. Efforts should be directed at early detection of development of third-generation resistance in hospitalized patients through careful clinical monitoring and at prevention of development of resistance through judicious use of antimicrobial agents.

Accepted for publication May 8, 2001.

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This study was supported in part by an unrestricted educational grant from Merck & Co., Inc, Whitehouse Station, NJ.

This work was presented in part at the 40th International Conference on Antimicrobial Agents and Chemotherapy, Toronto, Ontario, September 19, 2000.

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